THE CLAIMS

What is claimed is:

1. An in vitro screening assay for antagonists of FGFR-mediated malignant cell transformation comprising the steps:

(i) providing a stable cell line genetically engineered to express a recombinant fibroblast growth factor receptor (FGFR) selected from FGFR1, FGFR2 and FGFR3, wherein the malignant potential of said cell line is modulated by said FGFR;

(ii) subjecting said cell line of (i) to treatment with the corresponding FGF ligand and a candidate antagonist; and

(iii) measuring an FGFR downstream signaling event,

wherein an antagonist is identified by suppressing said FGFR downstream signaling event.

2. The screening assay of claim 1 wherein the FGFR downstream signaling event is selected from:

(a) FGFR tyrosine phosphorylation;

(b) activation of one or more intracellular proteins involved in signal transduction pathways of receptor tyrosine kinases selected from STAT1, JNK, PLCγ, ERK, STAT5, PI3K, PKC, FRS2 and/or GRB2; and/or

(c) a cell differentiation-related effect.

3. The screening assay of claim 1 wherein the FGFR is FGFR3, the cells are treated with FGF9 and a candidate antagonist, and the downstream signaling event is activation of JNK, and the antagonist inhibits said JNK activation.

4. The screening assay of claim 1 wherein the FGFR downstream signaling event is a cell differentiation-related effect selected from cell aggregation, formation of nodules and/or formation of cartilage, said effect being detected by light microscopy, turbidimetry, or flow cytometry.

5. The screening assay of claim 1 wherein the FGFR downstream signaling event is a cell differentiation-related effect being a change in the expression at RNA or protein levels of a marker of cell differentiation selected from bone sialoprotein, matrilin-3, type X collagen, 4-1BB, ILA, type II collagen and/or MGP.

6. The screening assay of claim 1, wherein the cell line is genetically engineered by transfection or infection with an expression vector containing a DNA encoding the wild type FGFR1, FGFR2 or FGFR3 or a constitutively active mutant thereof.

7. The screening assay of claim 6, wherein said cells are transfected or infected with an expression vector containing a DNA encoding the wild type FGFR1, FGFR2 or FGFR3.

8. The screening assay of claim 6, wherein said cells are transfected or infected with an expression vector containing a DNA encoding a constitutively active mutant FGFR1, FGFR2 or FGFR3.

9. The screening assay of claim 8, wherein said cells are transfected or infected with an expression vector containing a DNA encoding the constitutively active mutant FGFR3 comprising the G380R substitution.

10. The screening assay of claim 6, wherein said wild type or mutant FGFR is expressed in said genetically engineered cells under the control of a non-regulatable promoter.

11. The screening assay of claim 6, wherein said wild type or mutant FGFR is expressed in said genetically engineered cells under the control of a regulatable promoter.

12. The screening assay of claim 11, wherein the regulatable promoter is selected from a tetracycline-responsive and a tetracycline- repressible promoter.

13. The screening assay of claim 1, wherein said cell line is derived from muscle tissue.

14. The screening assay of claim 13, wherein the cell line is a myoblast cell line.

15. The screening assay of claim 14, wherein the cell line is derived from the L8 myoblast cell line.

16. The screening assay of claim 15, wherein the L8 myoblast cell line is genetically engineered by transfection or infection with an expression vector containing a DNA encoding the wild type FGFR3 or the constitutively active mutant FGFR3 comprising the G380R substitution.

17. The screening assay of claim 1, wherein said cell line is derived from a chondrocyte cell line.

18. The screening assay of claim 17, wherein the chondrocyte cell line is derived from an RCJ cell.

19. The screening assay of claim 18, wherein the chondrocyte RCJ cell line is genetically engineered by transfection or infection with an expression vector containing a DNA encoding the wild type FGFR1, FGFR2, or FGFR3 or a constitutively active mutant thereof.

20. The screening assay of claim 18, wherein the chondrocyte RCJ cell line is genetically engineered by transfection with a plasmid or infection with a retroviral vector containing a DNA encoding the wild type FGFR3 or the constitutively active mutant FGFR3 comprising the G380R substitution.

21. The screening assay of claim 19, wherein the genetically engineered chondrocyte RCJ cell line expressing FGFR1, FGFR2 or FGFR3 is a cell line deposited at the CNCM under Accession Nos. I-2122, I-2123, I-2124, or I-2125, and progenies thereof.

22. An *in vivo* screening assay for antagonists of FGFR-mediated malignant cell transformation and tumor formation and progression, comprising the steps:

(i) providing a stable cell line genetically engineered to express a recombinant wild type or constitutively active mutant fibroblast growth factor receptor (FGFR)

selected from FGFR1, FGFR2 and FGFR3, wherein the malignant potential of said cell line is modulated by said FGFR;

(ii) implanting or injecting said cells of (i) expressing said recombinant FGFR into a non-human animal;

(iii) administering a candidate antagonist to said animal, either concomitantly with said cells of step (ii) or thereafter; and

(iv) evaluating the formation of tumors in said animal,

wherein an antagonist is identified as a suppressor of FGFR-induced tumor formation and progression or as an enhancer of FGFR-suppressed tumor formation and progression.

23. The *in vivo* screening assay of claim 22, wherein the animal is a mammal.

24. The *in vivo* screening assay of claim 23, wherein the mammal is a mouse.

25. The *in vivo* screening assay of claim 23, wherein the immune system of said mammal is deficient in one or more aspects.

26. The *in vivo* screening assay of claim 25, wherein the animal is a SCID or nude mouse.

27. The *in vivo* screening assay of claim 26, wherein genetically engineered rat myoblast L8 cells expressing a recombinant constitutively active mutant FGFR selected from FGFR1, FGFR2 or FGFR3, are implanted or injected into a nude mouse, and the FGFR-induced tumor formation and progression of said FGFR-expressing L8 cells is inhibited by administration of an inhibitor of FGFR to the mouse thus causing a decrease in tumor formation and progression in the mouse.

28. The *in vivo* screening assay of claim 27, wherein said genetically engineered rat myoblast L8 cells express the recombinant constitutively active mutant G380R FGFR3.

29. The *in vivo* screening assay of claim 28, wherein said genetically engineered myoblast L8 cells are the cells herein designated L8-hAchR3, deposited at the CNCM under Accession No. I-2382.

30. The *in vivo* screening assay of claim 26, wherein genetically engineered rat chondrocyte RCJ cells expressing a recombinant wild type or constitutively active mutant FGFR1, FGFR2, or FGFR3, are implanted or injected into a nude mouse, and the FGFR-suppressing tumor formation of said FGFR-expressing RCJ cells is inhibited by administration of an inhibitor of FGFR thus causing an increase in tumor formation and progression.

31. The *in vivo* screening assay of claim 30, wherein said genetically engineered rat chondrocyte RCJ cells express the recombinant constitutively active G380R mutant FGFR3.

32. The *in vivo* screening assay of claim 29, wherein said genetically engineered rat chondrocyte RCJ cells are cells expressing the G380R mutant FGFR3, wild type FGFR1, wild type FGFR2, and wild type FGFR3, herein designated RCJ-13 M14, RCJ-13 R1-1, RCJ-13 R2-2, and RCJ-13 W11, respectively, deposited at the CNCM under Accession Nos. I-2122, I-2123, I-2124, and I-2125, respectively.

33. A stable cell line whose malignant phenotype is modulated by a FGFR selected from FGFR1, FGFR2 and FGFR3, said cell line being selected from genetically engineered rat myoblast L8 cells and rat chondrocyte RCJ cells expressing a recombinant wild type or constitutively active mutant FGFR1, FGFR2 and FGFR3 under a regulatable or a non-regulatable promoter, and progenies thereof.

34. The stable cell line according to claim 33, wherein said cells are genetically engineered rat myoblast L8 cells expressing the wild type FGFR3 and the G380R mutant FGFR3, herein designated L8-hWTR3-34 and L8-hAchR3, respectively, and deposited at the CNCM under Accession Nos. I-2381 and I-2382, respectively, and progenies thereof.

35. The stable cell line according to claim 33, wherein said cells are genetically engineered rat chondrocyte RCJ cells expressing the G380R mutant FGFR3, wild type FGFR1, wild type FGFR2, and wild type FGFR3, herein designated RCJ-13 M14, RCJ-13 R1-1, RCJ-13 R2-2, and RCJ-13 W11, respectively, deposited at the CNCM under Accession Nos. I-2122, I-2123, I-2124, and I-2125, respectively, and progenies thereof.